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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,052	11/20/2001	Holger Bock	2727-154	8509

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EXAMINER	
YOUNG, JOSEPHINE	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 02/25/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,052	BOCK ET AL.	
	Examiner	Art Unit	
	Josephine Young	1623	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 6-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

A written description analysis involves three principle factors:

(1) field of the invention and predictability of the art,

(2) breath of the claims, and

(3) possession of the claimed invention at the time of filing for each claimed species/genus.

The claims are directed to boronated or phosphorylated peptide nucleic acids, which may be used to increase the hydrophilicity of therapeutic peptide nucleic acids to improve the ability of such therapeutic peptide nucleic acids to permeate into cells. The specification never provides any evidence that such property exist for the claimed compounds. A statement of a potential effect does not constitute a sufficient written description for the utility of said compounds; moreover, the support in the specification is not adequate for the claim to the treatment of cancer.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by functional characteristics sufficient to show the Applicant was in possession of the claimed genus. There are a variety of boronated or phosphorylated compounds each with a certain degree of hydrophilicity, reactivity and toxicity for which there is not seen support for using said compounds in the instant disclosure, and in particular for cancer therapy. There is limited predictability in the art that any one compound or class of compounds is capable of increasing the hydrophilicity and treating cancer from a variety of boronated or phosphorylated products. To provide adequate support for the breadth of the claims, Applicant would have to establish that a distribution of compounds imparts increased hydrophilicity and ability to treat a variety of cancers. An adequate representation of species requires that the species that are expressly described be representative of the entire genus and what constitutes a "representative number" is an inverse function of the predictability of the art. As such, there is not seen any data that supports Applicant's claim that at the time of filing, the use of the compounds of the invention was applied could promote increased permeability into cells or could treat cancer.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below in In re Wands USPQ2d 14000. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention.

These factors include

(1) quantity of experimentation necessary,

(2) the amount of guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the predictability of the art and

(7) the breath of the claims.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which cells or cancer lines would be effected by the boronated or phosphorylated

peptide nucleic acid sequence for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing and determining such, as no boronated or phosphorylated peptide nucleic acid sequence was assessed for any form or cancer.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, while certain agents and compositions are known to treat certain forms of cancer, no effective agent or composition has been found for the treatment of all cancer types. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the compounds needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that since there are no working examples of the treatment of cancer using the boronated or phosphorylated peptide nucleic acid sequence of the present invention, it is seen that there is not sufficient guidance in the specification to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The compound of the formula "W-U-Z" in claim 1 renders the claims in which it appears indefinite. It is unclear as to if the formula represents only one W, U and Z as in claim 1, or if the formula is meant to represent multiple units of W, U and Z as claim 2 would suggest.

The term "amino acid unit" and "PNA unit" in claim 1 renders the claims in which it appears indefinite. It is unclear as to how the units are attached to other variables within the compound of the formula W-U-Z.

The term "exhibits" in claim 1 renders the claims in which it appears indefinite. It is unclear as to how a variable can exhibit a particular moiety.

Claim 9 is rejected, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the conversion of a compound of formula II to a compound as defined in claim 1. It is unclear as to how to convert the compounds in "known matter".

Claim 10 is rejected, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. While the preamble of the claim indicates that the claim is a method claim, there are no method steps.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article EGHOLM, et al, J. Am. Chem. Soc., 1992, 114, 1895-1897 (U) and the article VARADARAJAN (W) and the article KANE et al., J. Org. Chem, 1993, 58, 991-992 (V).

Applicant claims boronated or phosphorylated peptide nucleic acids, methods to make such compounds and boronated or phosphorylated synthetic intermediates.

EGHOLM teaches that peptide nucleic acids (PNAs) are molecules where the individual nucleobases are linked to an achiral peptide backbone. See page 1895, third paragraph.

EGHOLM does not teach that the PNAs can be boronated or phosphorylated to increase hydrophilicity.

VARADARAJAN teaches that boron can be attached to peptides via the alpha carbon of the amino acids. See Scheme I on page 247. Further, on page 342, last sentence of the first paragraph, VARADARAJAN discloses that the hydrophilicity of peptides can be markedly increased using anionic [*nido*-7,8-$C_2B_9H_{11}$]$^-$ moieties.

KANE teaches that hydrophilic amino acids, such as phosphorylated serine, can increase the hydrophilicity of the derived peptides. See page 992, right column, first full paragraph. KANE also teaches a method of synthesis of boronated peptides and useful boronated intermediates. See Schemes III and IV on page 992

It would have been obvious to one of ordinary skill in the art to increase the hydrophilicity of a peptide nucleic acid via the boronation or phosphorylation of the peptide backbone, as both VARADARAJAN and KANE teach that such hydrophilic species would increase the hydrophilicity of the peptide chain. A skilled artisan would have been motivated and had a reasonable expectation of success to make such compounds by combining the PNA synthetic techniques of EGHOLM with the boronated synthesis of KANE.

Claims 1-3, 5 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over US patent 5,846,741 to GRIFFITHS et al. (A) in view of the article, VARADARAJAN et al., Bioconjugate Chem., **1991**, *2*, 242-253 (W).

Applicant claims boronated peptide nucleic acids and methods to use such compounds in cancer therapy.

GRIFFITHS teaches in col. 2, lines 42-43 that boronated amino acids have been used to treat melanoma cells. Further, in col. 4, lines 11-33, GRIFFITHS discloses methods to selectively deliver boron-containing compounds using a first member of a binding pair and a complementary member of the binding pair and boron atoms (i.e. a boron-containing compound). In col. 6, line 28-35, GRIFFITHS teaches that the binding pair can be complementary polynucleotides fragments, including DNA, RNA and synthetic analogs of

polynucleotides such as PNAs. In col. 5, lines 17-35, GRIFFITHS specifically discloses that the compositions can be used to treat tumors in targeted BNCT.

GRIFFITHS does not specifically disclose where the boron atoms would be attached to the PNA.

As set forth supra, VARADARAJAN teaches that boron can be attached to peptides via the alpha carbon of the amino acids. See Scheme I on page 247.

It would have been obvious to one of ordinary skill in the art to make the boronated PNAs of GRIFFITHS via the methodology of VARADARAJAN for targeted BNCT for the treatment of tumors. A skilled artisan would have been motivated and had a reasonable expectation of success to boronate the amino acids of the peptide nucleic acid as such manipulation was well known in the art, as shown by VARADARAJAN.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Claims 1-10 are pending. Claims 1-10 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
February 24, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
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